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Reversibility of Cardiac Abnormalities in Human Immunodeficiency Virus (HIV)-Infected Individuals: A Serial Echocardiographic Study

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Seventy adults who tested positive for human immunodeficiency virus (HIV) were prospectively studied with serial echocardiography to better define the prevalence and progression of cardiac disease in such patients. Fifty outpatients (Group A), including 44 with acquired immunodeficiency syndrome (AIDS) and 6 with AIDS-related complex, and 20 additional patients (Group B) with asymptomatic HIV infection had baseline echocardiographic studies at a time when no patient had symptomatic heart disease. Follow-up studies were performed at 9 ± 3 months in 52 patients (74%) and again at 15 ± 3 months after baseline studies in 29 patients (41%). During the study, 22 patients (44%) in Group A and 1 patient (5%) in Group B died.

Cardiac abnormalities were noted in 26 patients (52%) in Group A and 8 patients (40%) in Group B (p = NS) on initial or follow-up study. An abnormal left ventricular ejection fraction (<45%) or fractional shortening (<28%) was seen in seven patients in Group A; of these, three had normal left ventricular function on a later echocardiogram. One patient in Group B had persistent left ventricular dysfunction. All patients in Group A with left ventricular dysfunction on two serial studies died within 1 year after the initial echocardiogram. Ejection fraction did not change between baseline and two follow-up studies in either group (A: 52 ± 9 vs. 56 ± 9 vs. 55 ± 5%, p = NS; B: 58 ± 6 vs. 58 ± 5 vs. 59 ± 6%, p = NS). Right-sided cardiac enlargement resolved in 18 patients (44%), including 5 of 10 in Group A and 3 of 8 in Group B. Pericardial effusions resolved without specific intervention in 5 (42%) of 12 patients in Group A and 2 (50%) of 4 in Group B. Analysis of CD4 counts revealed no relation with the presence of left ventricular dysfunction or right-sided cardiac enlargement. In patients with AIDS with pericardial effusion, however, CD4 counts were significantly lower (68 ± 74/mm^3) than in those without effusion (290 ± 248/mm^3, p < 0.001).

Thus, echocardiographic abnormalities are common in asymptomatic outpatients with HIV infection, and persistent left ventricular dysfunction portends an especially grim prognosis in patients with AIDS. Some of these abnormalities, including left ventricular dysfunction, right-sided cardiac enlargement and pericardial effusion, are transient in nature and are not consistently associated with clinically apparent intercurrent illnesses. These findings have important implications for future studies involving therapy for AIDS-associated heart disease.

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Several groups (1–22) have described the occurrence of human immunodeficiency virus (HIV)-associated cardiac abnormalities in both pathologic and clinical studies. These studies report a widely variable prevalence of cardiac lesions among patients infected with HIV, depending on the patient group selected and the methods used. Studies (6,7,14) of patients with asymptomatic HIV infection note a relatively low frequency of left ventricular dysfunction and other abnormalities, while many autopsy studies (2–4,15) in patients with the acquired immunodeficiency syndrome (AIDS) report higher percentages of cardiac lesions, including lymphocytic myocarditis, left ventricular enlargement, cardiac Kaposi's sarcoma and myocardial fibrosis. Recent echocardiographic studies (6,7,9,11,14,22) found abnormalities, including pericardial effusion, biventricular enlargement and dysfunction, cardiac masses and mitral valve prolapse, in 0% to 70% of various patient groups. No serial studies are available, however, to assess the progression of HIV-associated cardiac disease in adults. Therefore, we prospectively studied groups of HIV-infected individuals with serial echocardiography to better define the prevalence of cardiac lesions in these patients and, more important, to assess the evolution of these abnormalities.

Methods

Study patients. The study included 70 patients (69 men, 1 woman) with HIV who were enrolled consecutively between January 1987 and June 1989. Patients were enrolled if they were willing to participate in the study and were ambulatory outpatients. None of those enrolled were intravenous drug abusers, although such patients were not excluded from the

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study. Mean patient age (±SD) was 38.1 ± 9.3 years (range 24 to 64). The patients were divided into two groups: Group A consisted of 50 patients with AIDS (n = 44) or AIDS-related complex (n = 6); Group B consisted of 20 patients with asymptomatic HIV infection. No patient had symptomatic heart disease at the beginning of the study, and all patients were followed up by the California Cooperative Treatment Group at the University of California, San Diego. All patients in Group A were being treated with the antiretroviral drug azidothymidine (or zidovudine, AZT) except three who were enrolled in 1987 and died before 1988. The majority of Group B patients were taking AZT during the study period: 11 were taking AZT, 8 were taking AZT or a placebo (this protocol code has not yet been broken), and 1 patient was lost to follow-up.

Study protocol. The study protocol consisted of baseline echocardiography and follow-up echocardiography, at ≥6 month intervals, as approved in 1986 by the Human Subjects Committee at the University of California, San Diego.

The hospital and protocol charts of all patients were analyzed for height and weight at initial evaluation, drugs and other intervention (for example, pericardiocentesis), protocol (if available), illness during the study period, cause and date of death (if applicable) and serial CD4 counts. CD4, previously known as T4, is a T lymphocyte antigenic marker recognized to correlate with prognosis and susceptibility to opportunistic infections in individuals with HIV (23). In the University of California, San Diego immunology laboratory, the CD4 count for normal patients ranges from 500/mm^3 to 1,200/mm^3.

Echocardiography. Quantitative M-mode, two-dimensional and Doppler echocardiograms were performed on a Hewlett-Packard Sonos 500 or 1000 ultrasound instrument. Standard views in the supine or left lateral decubitus position were obtained. Variables analyzed included left ventricular end-diastolic and end-systolic diameter, fractional shortening and left atrial size on M-mode, as well as left ventricular end-diastolic and end-systolic areas and right ventricular end-diastolic area on two-dimensional echocardiography. The echocardiograms were also reviewed for the presence of left and right atrial enlargement, valvular vegetations and abnormalities, mitral valve prolapse (defined as prolapse of either mitral valve leaflet behind the level of the mitral anulus on parasternal, long-axis view) (24), pericardial effusions and intracardiac masses.

End-diastolic and end-systolic areas of the left ventricle, as well as the end-diastolic area of the right ventricle, were digitized on a computer grid in the apical four-chamber view. Left ventricular volumes and ejection fraction were calculated by an off-line analysis system that utilizes a modified Simpson's rule (25,26). Volumes were corrected for body surface area. In our study the lower limit of normal value was 45% for ejection fraction and 28% for fractional shortening. These limits, similar to those in a previous study (14), were chosen to avoid labeling borderline normal values as abnormal. A normal value for right ventricular area was defined as 12 to 26 cm^2 (27) and a normal value for left ventricular end-diastolic volume index as <80 ml/m^2 (26). To assess inter- and intraobserver variability, 10% of echocardiograms were chosen randomly and reanalyzed by two of the investigators.

Table 1. Patients With Cardiac Abnormalities on Any Study

	Group A (n = 50)	Group B (n = 20)	Total (70)
Any abnormality	26 (52%)	8 (40%)	34 (49%)
Mitral valve prolapse (MVP)	5 (10%)	2 (10%)	7 (10%)
Excluding MVP as sole abnormality	24 (48%)	7 (35%)	31 (44%)
Left ventricular dysfunction (EF <45%, FS <28%)	7 (14%)	1 (5%)	8 (11%)
Right-sided cardiac enlargement	10 (20%)	7 (35%)	17 (24%)
Pericardial effusion	11 (22%)	4 (20%)	15 (21%)

Data are expressed as number and, in parentheses, percent of patients with an abnormality. EF = ejection fraction; FS = fractional shortening; Group A = 44 patients with acquired immunodeficiency syndrome (AIDS) and 6 patients with AIDS-related complex; Group B = 20 patients with asymptomatic HIV infection.

Statistical analysis. Data were evaluated by chi-square test, Fisher's exact test and Student's *t* test. Comparisons were made between Groups A and B (patients with AIDS and AIDS-related complex vs. those with asymptomatic HIV infection). Data are mean values ± SD. Differences between groups were considered significant at $p < 0.05$.

Results

Clinical course. Of the 70 initial patients, 52 (33 in Group A and 19 in Group B) had follow-up echocardiographic studies (the mean interval between studies was 9 ± 3 months, range 6 to 16 months). Between the baseline and first follow-up studies, 22% of patients in Group A died, and 12% were lost to follow-up. In Group B, 5% of patients were lost to follow-up. A second follow-up study was done in 29 patients (18 in Group A, 11 in Group B) at a mean interval of 15 ± 3 months (range 12 to 21) after the baseline study. Between the first and second follow-up echocardiograms, an additional 22% of Group A patients died and 8% were lost to follow-up. In Group B, 5% of the patients died and 35% were either lost to follow-up or have studies pending at this time.

Echocardiographic abnormalities (Table 1). Overall, echocardiographic abnormalities were identified in 49% of patients on one or more studies (52% in Group A and 40% in Group B). Mitral valve prolapse was noted in five Group A patients (10%) and two Group B patients (10%). Excluding those patients whose only echocardiographic lesion was mitral valve prolapse, abnormalities were present in 44% of all patients (48% of patients in Group A and 35% in Group B).

Group A (Fig. 1). Mean ejection fraction did not change significantly between studies (52 ± 9% vs. 56 ± 9% vs. 55 ±

5%, p = NS). Left ventricular end-diastolic volume index also did not change significantly (57 ± 12 vs. 54 ± 14 vs. 56 ± 18 ml/m^2, p = NS). An abnormal left ventricular ejection fraction or fractional shortening was initially seen in 6 of 33 patients with serial studies, but in only 3 of those 6 at follow-up study (Fig. 1A). One patient with an initially normal ejection fraction had new global hypokinesia and an ejection fraction of 44% on the second follow-up study. While most patients with a low ejection fraction were in poor health, none were limited by congestive heart failure symptoms as such and none required medical therapy for cardiac symptoms. Of the seven patients with left ventricular dysfunction in Group A, three had a normal left ventricular ejection fraction documented on a subsequent echocardiogram. All three patients with persistently abnormal left ventricular function on serial echocardiograms died within 1 year after the baseline study.

Seven patients in Group A had right-sided cardiac enlargement initially (Fig. 1B). The first follow-up study showed resolution of this abnormality in four of these seven, while two new cases of right ventricular enlargement were found. On the second follow-up study, one new case of right ventricular enlargement was present. Of the five patients with right ventricular enlargement on the first follow-up study, one had resolution of the abnormality, one was lost to follow-up and three died before the final examination. Of the 10 patients with right-sided cardiac enlargement in Group A, 5 (50%) had normal right heart size on a subsequent study.

Review of all available patient charts revealed that four Group A patients had Pneumocystis carinii *pneumonia* diagnosed within 1 month before or after an echocardiogram that demonstrated right ventricular enlargement. In addition, three of these patients had normal right ventricular size on subsequent studies after the pneumonia was treated. However, the remaining six patients with right ventricular enlargement had no documented pulmonary infection at or near the time of echocardiography.

Pericardial effusion was found initially in six Group A patients, but in only one of the six on follow-up study. None of the initial effusions were associated with cardiac tamponade, and none of these patients underwent pericardiocentesis. Five new effusions were seen on the first follow-up study, including two in patients with echocardiographic evidence of impending cardiac tamponade (right atrial and right ventricular diastolic collapse). One of these patients underwent pericardiocentesis with immediate improvement in right ventricular filling; both patients later died before a second follow-up study was performed. A review of patient charts showed an intercurrent febrile illness associated with a pericardial effusion in one patient and an episode of asymptomatic left ventricular enlargement in another. In the remaining patients with pericardial effusion, no significant intercurrent illnesses were noted. Of the six patients with effusion on the first follow-up study, four died before a second follow-up echocardiogram, and the remaining two had persistent effusion on the final studies. No effusions were large at baseline or showed evidence of tamponade. Without specific treatment, 5 (42%) of 12 pericardial effusions in Group A resolved by the time of a later echocardiogram.

Group B (Fig. 2). Mean left ventricular ejection fraction did not change between studies (58 ± 6% vs. 58 ± 5% vs. 59 ± 6%, p = NS), and no patient had an ejection fraction <45% (Fig. 2A). Serial left ventricular end-diastolic volume indexes were also similar among studies (50 ± 6 vs. 53 ± 15 vs. 52 ± 10 ml/m^2, p = NS). One patient had evidence on the initial study of left ventricular dysfunction (fractional shortening 14%) that persisted on follow-up study, although serial ejection fractions were in the normal range (47% and 49%).

One Group B patient had right ventricular enlargement at baseline that resolved by the time of the first follow-up study, but five other patients had right ventricular enlargement at that time (Fig. 2B). Of these five, one developed AIDS and later died (the same patient who also developed a pericardial effusion). Soon after his final echocardiogram, this patient had aspiration pneumonitis and multiorgan system failure. Two patients had normal right heart size on the second follow-up echocardiogram, and two were lost to follow-up. On the second follow-up study, right ventricular enlargement was found in two patients for the first time. Therefore, among the eight patients with right ventricular enlargement in Group B, the enlargement had resolved in three (38%) on follow-up studies.

Pericardial effusion was seen in three patients initially, but in only one patient by the time of the first follow-up study. On the second follow-up study, one new effusion was detected in the patient who developed AIDS. Excluding this patient, no association was found between systemic illness and pericardial effusion. None of the pericardial effusions observed in Group B were clinically or hemodynamically significant, and no pericardiocenteses were performed. In summary, half of the four effusions seen in Group B had resolved by the time of follow-up echocardiograms.

CD4 counts. In this study, no significant relation was found between CD4 counts and left ventricular dysfunction or right ventricular enlargement. In Group A, the mean CD4 count in patients with left ventricular dysfunction was 198 ± 82/mm^3 versus 249 ± 255/mm^3 in those with normal left ventricular function (p = NS by Fisher's exact test). However, in Group A patients with echocardiographically proved pericardial effusion, CD4 counts (drawn at or near the time of echocardiography) were significantly lower (68 ± 74/mm^3) than in patients without effusion (290 ± 248/mm^3, $p < 0.001$ by Fisher's exact test).

Observer variability. Reanalysis was performed of 10% of echocardiographic studies chosen at random. Inter- and intraobserver variability was <10% on M-mode measurements and measurement of left ventricular ejection fraction and right ventricular end-diastolic area. Observer variability was 0% in studies of patients with pericardial effusion.

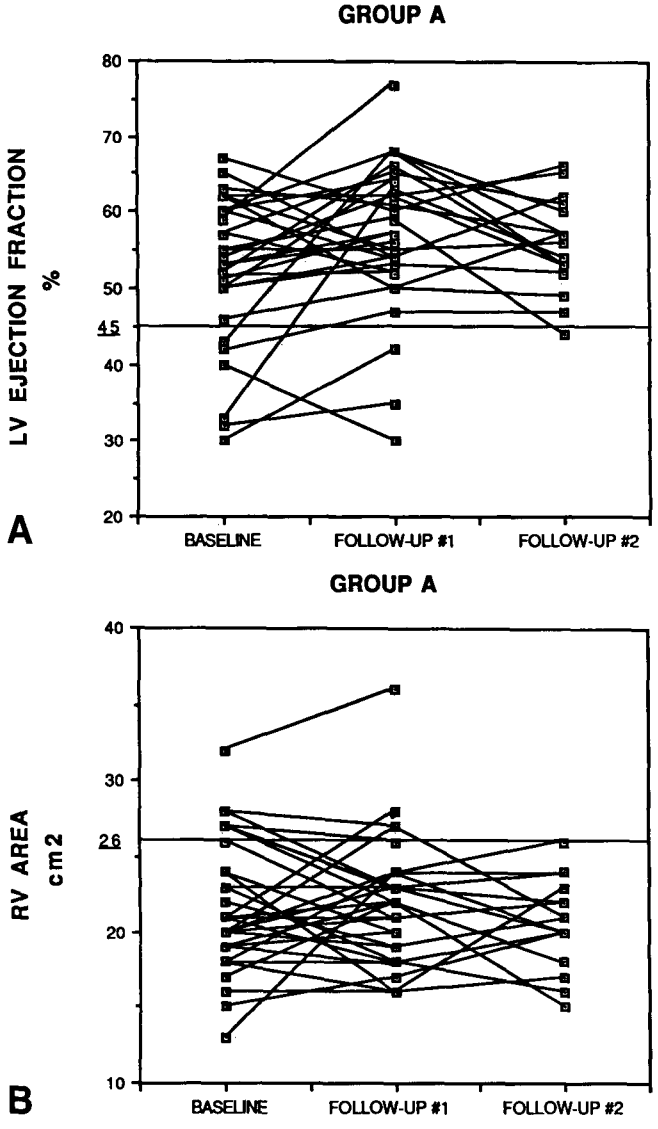

Figure 1. Echocardiographic results for patients in Group A (44 patients with acquired immunodeficiency syndrome [AIDS] and 6 with AIDS-related complex). **A,** Left ventricular (LV) ejection fraction at baseline and at first and second follow-up. The cutoff for a normal value is depicted by the **horizontal line**, with all values >45% considered normal. **B,** Right ventricular (RV) areas at baseline and at first and second follow-up. As depicted by the **horizontal line**, all values <26 cm^2 are considered normal.

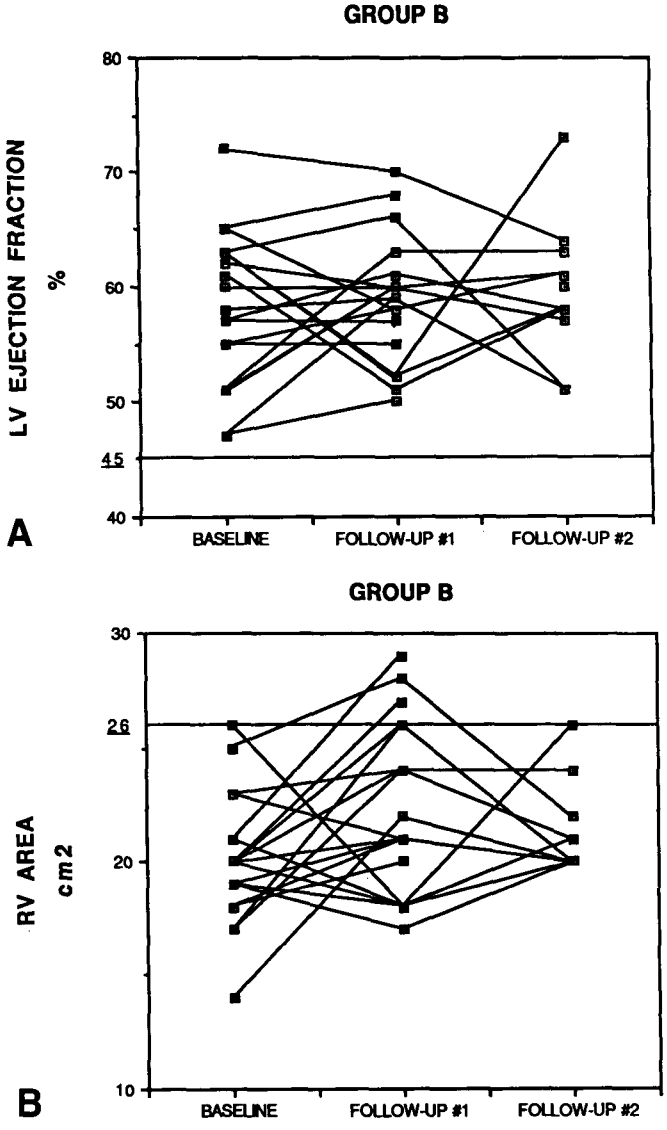

Figure 2. Echocardiographic results for patients in Group B (20 patients with asymptomatic human immunodeficiency virus infection. **A,** Left ventricular (LV) ejection fraction at baseline and at 1st and 2nd follow-up. The cutoff for a normal value is depicted by the **horizontal line**, with all values >45% considered normal. **B,** Right ventricular (RV) areas at baseline and at first and second follow-up. As depicted by the **horizontal line**, all values <26 cm^2 are considered normal.

Discussion

Cardiac manifestations of AIDS. Recent studies have shown that, in addition to the pulmonary, gastrointestinal and neurologic complications of AIDS, cardiac manifestations are not rare, occurring in approximately 40% of patients (28). Both antemortem and pathologic reports have documented a sizable incidence of cardiac abnormalities, many of which are asymptomatic or clinically unsuspected at the time of discovery. While the prevalence of cardiac involvement in AIDS has been studied by several investigators, there is little information on the evolution of HIV-associated cardiac disease, particularly in ambulatory patients. Observations on the echocardiographic progression of cardiac abnormalities in children have recently been published (19), but no such reports are currently available for adults. Our prospective study was designed to address this issue.

Fifty patients with AIDS or AIDS-related complex (Group A) and 20 patients with asymptomatic HIV infection (Group B) were followed up for up to 21 months after baseline echocardiography. Overall, 48% of patients had an abnormality on one or more echocardiograms. Although Group A had a higher percentage of patients with abnormal studies (52% vs. 40%), the difference was not statistically significant. Fourteen percent of Group A and 5% of Group B

Table 2. Previous Studies of Cardiac Function in HIV-Infected Patients

Author (reference)	HIV Diagnosis (n)	% of Patients With Abnormal Echocardiogram			
		Total	LV	RV	PE
Corallo et al. (6)	All AIDS (102)*	54	54	NA	38
Fink et al. (1)	All AIDS (15)	66	20	13	40
Hecht et al. (9)	All AIDS (27)	48	30	NA	26
Himelman et al. (14)	(51 AIDS, 19 HIV+)	27	11	NA	10
Kinney et al. (22)	(15 AIDS, 24 ARC)	>47§;>21‖	15	NA	31
Levy et al. (11)	(35 AIDS, 25 HIV+)	35	15	NA	30
Monsuez et al. (7)	(43 AIDS, 43 ARC)	100†; 54‡	33†; 19‡	NA; NA	72†; 7‡
Raffanti et al. (8)	All AIDS (12)	42	17	25	8
Reitano et al. (21)	(21 AIDS, 4 ARC)	40	12	24	28

Studies are listed alphabetically; the percent of patients with symptoms of heart disease varied from 0% to 14%. *Three of the 102 patients had a cardiac mass; †indicates patients with cardiac symptoms; ‡indicates patients without cardiac symptoms; §of patients with AIDS; ‖of patients with ARC. AIDS = acquired immune deficiency syndrome; ARC = AIDS-related complex; HIV+ = human immunodeficiency virus infection, without AIDS; LV = left ventricular dysfunction/enlargement; NA = not available; PE = pericardial effusion; RV = right ventricular enlargement.

patients had evidence of left ventricular dysfunction ($p = 0.27$). The incidence of pericardial effusion and right-sided cardiac enlargement was approximately the same in both groups, although the only effusions causing hemodynamic compromise were seen in Group A. That no patient in either group had valvular vegetations may be due in part, to the absence of intravenous drug users in the study. Drug users were not intentionally excluded from the study, but the great majority of patients followed by the California Cooperative Treatment Group at this institution are homosexual men without a history of drug abuse. Although our patient cohort, therefore, does not represent the entire spectrum of individuals with HIV infection, the echocardiographic abnormalities noted may better portray the true effects of HIV infection and AIDS, without the confounding influence of intravenously injected contaminants, intermittent bacteremia and prior episodes of endocarditis.

Analysis of CD4 counts revealed no association with abnormal left ventricular function. However, there was a significant correlation between a low CD4 count and the presence of a pericardial effusion.

Comparison with previous reports. Overall, our prevalence results are similar to those of previous reports of HIV-associated cardiac disease (Table 2). In an echocardiographic study of 102 patients, Corallo et al. (6) reported a 54% incidence of cardiac abnormalities and left ventricular dysfunction. In patients similar to ours (without cardiac symptoms at baseline), Monsuez et al. (7) found a 54% incidence of abnormalities, including left ventricular dysfunction in 18% and pericardial effusion in 7%. Levy et al. (11) reported a 35% incidence of cardiac lesions in a group consisting of patients with AIDS and patients with asymptomatic HIV infection. They found a correlation between unspecified cardiac abnormalities and low CD4 counts: in AIDS patients with CD4 counts $<100/mm^3$, the prevalence of echocardiographic abnormalities was significantly higher (12 of 22, 55%) than in those with CD4 counts $>100/mm^3$ (1 of 14, 7%, $p < 0.01$) (11). The association between low CD4 counts and echocardiographic abnormalities was confirmed in our study, but only with respect to pericardial effusion. The study of Himelman et al. (14) of hospitalized and ambulatory HIV-positive patients reported an overall incidence of abnormalities lower than ours; these results may be related to the number of echocardiograms performed on each study patient—more than 70% of our patients had at least two examinations over time, and several patients with an initially normal echocardiogram had cardiac abnormalities on follow-up studies.

While our results confirm those of previous reports, the more important aspect of this study is the assessment of the evolution of HIV-related cardiac disease. Unexpectedly, a number of patients had cardiac abnormalities that were transient in nature. In Group A, left ventricular dysfunction resolved in 43% of patients by the time of a follow-up echocardiogram, as did right-sided cardiac enlargement in 50% and pericardial effusion in 42%. As stated earlier, no patient was limited by congestive heart failure symptoms, as such, and none was receiving maintenance treatment with digoxin, diuretics or afterload-reducing agents. No patient in either group had symptoms of pericarditis (although two patients in Group A had evidence of mild or impending tamponade).

Prognosis of left ventricular dysfunction. Analysis of Group A showed that left ventricular dysfunction on a single study did not necessarily portend an especially poor prognosis, but a persistently low left ventricular ejection fraction (present on two serial echocardiograms) was associated with a 100% mortality rate within 1 year ($n = 3$). In Group B, the only case of left ventricular dysfunction at baseline persisted on follow-up, and this patient remains alive 18 months later. However, by the time of later examination, right ventricular enlargement had resolved in 38% of patients and pericardial effusion had resolved in 50%.

It is unlikely that the results presented here are artifactual. A lower than usual abnormal ejection fraction break point (45%, the same as that in the study of Himelman, et al.

[14]) and a higher than usual abnormal right ventricular end-diastolic area (27) were chosen to avoid labeling borderline results as abnormal. Also, the changes in ejection fraction and right ventricular end-diastolic area in those patients who crossed the normal/abnormal break points were usually not subtle: in Group A, the average change in ejection fraction and right ventricular end-diastolic area of these patients was 40% and 22%, respectively. Similarly, in Group B, the change in right ventricular end-diastolic area crossing the same break point was 33%. All values were well outside the limits of inter- and intraobserver variability.

Pathogenesis of cardiac abnormalities. Why, then, are cardiac lesions in AIDS occasionally transient? In the case of left ventricular dysfunction, several possibilities exist. Recent studies (3,4,13,17) support infectious myocarditis as the probable cause of left ventricular dysfunction in patients with AIDS. Several viruses that are known to cause cardiomyopathies in humans may be transient, and a case of coxsackievirus B myocarditis in a patient with HIV with left ventricular enlargement was recently described (29).

It is also possible that HIV itself is cardiomyopathic. An intriguing possibility, therefore, is that AZT may improve left ventricular function in cases of HIV-associated cardiomyopathy. Indeed, all three patients with abnormal left ventricular ejection fraction in Group A who showed improvement on the first follow-up echocardiogram were taking AZT. However, the three patients whose left ventricular function did not improve from baseline (and the patient whose left ventricular function was depressed on the second follow-up examination) were taking AZT as well. Thus, our data are not sufficient to support AZT as an effective therapy for HIV-associated cardiomyopathy. Two other drugs commonly used in AIDS patients, co-trimoxazole and pentamidine, are not known to cause left ventricular enlargement or myocarditis, although the latter drug has been reported to cause prolongation of the QT interval and torsade de pointes (30). Zazzo et al. (31) have theorized that nutritional deficiencies may be linked to cardiomyopathy in AIDS. Although these may have contributed to the abnormalities seen, the close medical follow-up of our patients makes severe nutritional deficiencies somewhat unlikely.

Right-sided cardiac enlargement occurred along with left ventricular enlargement or hypertrophy in 33% of all cases, and of these, only one resolved (coincident with an improvement in left ventricular function). A possible explanation for episodic, isolated right ventricular enlargement in our AIDS patients is pulmonary hypertension secondary to pneumonia and hypoxia. Although this study was not designed to specifically address right ventricular size before and after pneumonia, it is logical that successful treatment of pulmonary infections and reversal of hypoxia could decrease right ventricular afterload and normalize right ventricular size. Although four patients with AIDS were diagnosed with *Pneumocystis carinii* pneumonia near the time of an echocardiogram that showed right ventricular enlargement, the majority of patients had no evidence of a recent or intercurrent pulmonary illness. Thus, hypoxia and pulmonary disease may account for some but not all cases of right ventricular enlargement in AIDS. Interstitial and restrictive lung disease as well as primary pulmonary hypertension have been observed (32,33) in patients with AIDS who have right ventricular enlargement and elevated pulmonary artery pressure. Although this type of lung disease may be responsible for some cases of right ventricular enlargement in our study, it is unlikely to have been present in all patients with transient right-sided cardiac abnormalities.

Opportunistic pulmonary infections did not occur in Group B patients (except in the one patient who developed AIDS during the study period), and the cases of transient, isolated right ventricular enlargement in this group are more difficult to explain. These patients may have had subclinical episodes of pulmonary disease, but the origin of right-sided cardiac abnormalities in this group is unclear and requires further study.

Infectious myocarditis and pericarditis probably account for a number of cases of transient pericardial effusion in our patients; hypoalbuminemia and contiguous pneumonic processes also may have played a role. No patient had radiation to the chest or had evidence of ischemic heart disease or myocardial infarction. Two cases of effusion in Group A and one in Group B occurred in the presence of left ventricular enlargement and dysfunction. Effusions were either small or moderate in size in all but two patients (in Group A), who had a large effusion and evidence of tamponade.

Limitations. There are several limitations to this study. First, follow-up is incomplete, typically because death occurred before follow-up echocardiography was performed (Group A), and contact was lost with patients (Group B). Follow-up examinations were scheduled at the beginning of the study to be conducted at least 6 months apart; therefore, several cases of cardiac abnormalities may have been missed in those patients who died just before follow-up echocardiograms were obtained. These limitations to follow-up may bias the results toward an underestimation of cardiac lesions. Second, the present study was not designed to include pathologic and autopsy correlation with echocardiographic findings; therefore, it is not possible to correlate antemortem echocardiographic manifestations with pathologically documented myocarditis, myocardial fibrosis, valvular lesions and ventricular enlargement. Although several pathologic reports are available (2,3,4,13,15) of AIDS and cardiac complications, this area merits further investigation.

Finally, as in all echocardiographic studies, intra- and interobserver variability may limit the reliability of our data. However, observer variability of ejection fraction and right ventricular end-diastolic area calculations was low (<10%), and nonexistent in cases of pericardial effusion. In addition, in those patients whose left ventricular ejection fraction or right ventricular size became normal or abnormal, the changes were rarely subtle, with mean differences substantially greater than the observer variability.

Clinical implications. Our study has several implications. First, although there are no truly "good" prognostic markers in this debilitating and ultimately fatal disease, the presence of left ventricular enlargement or dysfunction on a single echocardiogram may not be as ominous as previously thought, because the condition of some patients may improve over time. Therefore, a single low ejection fraction does not imply that further intervention will be completely unsuccessful. Second, because many abnormalities detected in our patients were not clinically suspected, we agree with Himelman et al. (14) that echocardiography should be considered early in patients with HIV infection who have dyspnea or vague chest complaints. Finally, it is unclear whether HIV itself is a cardiomyopathic agent, and our study does not lend support to either side of the debate. Our finding of transient cardiac abnormalities, however, has important implications for future studies involving therapy for AIDS-associated heart disease.

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References

1. Fink L, Reichek N, St John Sutton MG. Cardiac abnormalities in acquired immune deficiency syndrome. Am J Cardiol 1984;54:1161–3.
2. Cammarosano C, Lewis W. Cardiac lesions in acquired immune deficiency syndrome (AIDS). J Am Coll Cardiol 1985;5:703–6.
3. Baroldi G, Corallo S, Moroni M, et al. Focal lymphocytic myocarditis in acquired immunodeficiency syndrome (AIDS): a correlative morphologic and clinical study in 26 consecutive fatal cases. J Am Coll Cardiol 1988;12:463–9.
4. Anderson DW, Virmani R, Reilly JM, et al. Prevalent myocarditis at necropsy in the acquired immunodeficiency syndrome. J Am Coll Cardiol 1988;11:792–9.
5. Cohen IS, Anderson DW, Virmani R, et al. Congestive cardiomyopathy in association with the acquired immune deficiency syndrome. N Engl J Med 1986;315:628–30.
6. Corallo S, Mutinelli R, Moroni M, et al. Echocardiography detects myocardial damage in AIDS: prospective study in 102 patients. Eur Heart J 1988;9:887–92.
7. Monsuez JJ, Kinney EL, Vittecoq D, et al. Comparison among acquired immune deficiency syndrome patients with and without clinical evidence of cardiac disease. Am J Cardiol 1988;62:1311–3.
8. Raffanti SP, Chiaramida AJ, Sen P, Wright P, Middleton JR, Chiaramida S. Assessment of cardiac function in patients with the acquired immunodeficiency syndrome. Chest 1988;93:592–4.
9. Hecht SR, Berger M, van Tosh A, Croxson S. Unsuspected cardiac abnormalities in the acquired immune deficiency syndrome: an echocardiographic study. Chest 1989;96:805–8.
10. Webb JG, Chan-Yan C, Kiess MC. Cardiac dysfunction associated with the acquired immune deficiency syndrome. Clin Cardiol 1988;11:423–6.
11. Levy WS, Simon GL, Rios JC, Ross AM. Prevalence of cardiac abnormalities in human immunodeficiency virus infection. Am J Cardiol 1989; 63:86–9.
12. Corboy JR, Fink L, Miller WT. Congestive cardiomyopathy in association with AIDS. Radiology 1987;165:139–41.
13. Reilly JM, Cunnion RE, Anderson DW, et al. Frequency of myocarditis, left ventricular dysfunction and ventricular tachycardia in the acquired immune deficiency syndrome. Am J Cardiol 1988;62:789–93.
14. Himelman RB, Chung WS, Chernoff DN, Schiller NB, Hollander H. Cardiac manifestations of human immunodeficiency virus infection: a two-dimensional echocardiographic study. J Am Coll Cardiol 1989;13: 1030–6.
15. Lewis W. AIDS: cardiac findings from 115 autopsies. Prog Cardiovasc Dis 1989;32:207–15.
16. Acierno LJ. Cardiac complications in acquired immunodeficiency syndrome (AIDS): a review. J Am Coll Cardiol 1989;13:1144–54.
17. Levy WS, Varghese J, Anderson DW, et al. Myocarditis diagnosed by endomyocardial biopsy in human immunodeficiency virus infection with cardiac dysfunction. Am J Cardiol 1988;62:658–9.
18. Lipshultz SE, Chanock SP, Sanders S, Colan SD, Perez-Atayde A, McIntosh K. Cardiovascular manifestations of human immunodeficiency virus infection in infants and children. Am J Cardiol 1989;63:1489–97.
19. Stewart JM, Kaul A, Gromisch DS, Reyes E, Woolf PK, Gowitz MH. Symptomatic cardiac dysfunction in children with human immunodeficiency virus infection. Am Heart J 1989;117:140–4.
20. Kaminski HJ, Katzman M, Wiest PM, et al. Cardiomyopathy associated with the acquired immune deficiency syndrome. J Acquir Immune Defic Syndr 1988;1:105–10.
21. Reitano J, King M, Cohen H, et al. Cardiac function in patients with acquired immune deficiency syndrome (AIDS) or AIDS prodrome (abstr). J Am Coll Cardiol 1984;3:525.
22. Kinney EL, Brafman D, Wright RJ. Echocardiographic finding in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex (ARC). Cathet Cardiovasc Diagn 1989;16:182–5.
23. Masur J, Ognibene FP, Yarchoan R, et al. CD4 counts as predictors of opportunistic pneumonias in human immunodeficiency virus (HIV) infection. Ann Intern Med 1989;111:223–31.
24. Levine RA, Stathogiannis E, Newell JB, Harrigan P, Weyman AE. Reconsideration of echocardiographic standards for mitral valve prolapse: lack of association between leaflet displacement isolated to the apical four chamber view and independent echocardiographic evidence of abnormality. J Am Coll Cardiol 1988;11:1010–9.
25. Schiller NB, Acquatella H, Ports TA, et al. Left ventricular volume from paired biplane two-dimensional echocardiographs. Circulation 1979;60: 547–55.
26. Wahr DW, Wang YS, Schiller NB. Left ventricular volumes determined by two-dimensional echocardiography in a normal adult population. J Am Coll Cardiol 1983;1:863–8.
27. Weyman AE. Cross-Sectional Echocardiography. Philadelphia: Lea & Febiger, 1982:502.
28. Factor SM. Acquired immune deficiency syndrome: the heart of the matter. J Am Coll Cardiol 1989;13:1037–8.
29. Dittrich H, Chow L, Denaro F, Spector S. Human immunodeficiency virus, coxsackievirus, and cardiomyopathy (letter). Ann Intern Med 1988;108:308–9.
30. Bibler MR, Chou T, Tolzis RJ, Wade PA. Recurrent ventricular tachycardia due to pentamidine-induced cardiotoxicity. Chest 1988;94:1303–6.
31. Zazzo JF, Chalas J, Lafont A, et al. Is nonobstructive cardiomyopathy in AIDS a selenium deficiency-related disease? (letter). J Parenter Enteral Nutr 1988;12:537.
32. Himelman RB, Dohrmann M, Goodman R, et al. Severe pulmonary hypertension and cor pulmonale in the acquired immune deficiency syndrome. Am J Cardiol 1989;64:1396–9.
33. Coplan NL, Shimony RY, Ioachim HL, et al. Primary pulmonary hypertension associated with human immunodeficiency viral infection. Am J Med 1990;89:96–9.